PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MARIA A. TREVISAN
WOLF, GREENFIELD & SACK P.C
600 ATLANTIC AVENUE
BOSTON, MA 02210

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	28 FEB 2005
Applicant's or agent's file reference B0877.70027	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/15443	17 May 2004 (17.05.2004)	29 January 2004 (29.01.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61F 2/06, 2/00, 2/02, 13/00; A61M 5/00; C12N 5/00, 5/06, 5/08 and US Cl.: 623/1.1, 1.42, 11.11, 23.75; 424/422, 93.1, 93.7; 435/325, 366; 604/27

Applicant

BROWN UNIVERSITY

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Initials
Confirmation ☐
Docketing ☑ LA
05/28/05 ✓

DOCKETED
MAR 0 4 2005

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Michael Wityshyn
DEBORAH A. THOMAS
PARALEGAL SPECIALIST
~~GROUP 1300~~
Telephone No. 571-272-1600

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1, 3-10, 12, 15-26, 31-41, 43	YES
	Claims 2, 11, 13-14, 27-30, 42	NO
Inventive step (IS)	Claims 8, 18-20, 25-26, 31-38, 41, 43	YES
	Claims 1-7, 9-17, 21, 22-24, 27-30, 39-40, 42	NO
Industrial applicability (IA)	Claims 1-43	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 36 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof:
Amyotrophic Lateral Sclerosis and Multiple Sclerosis should be written out completely instead of using the abbreviations.

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10/587884

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 2, 11, 13-14, 27-30 and 42 lack novelty under PCT Article 33(2) as being anticipated by Murayama et al (Exp Hematol, 2002).

Murayama et al teach a method of isolating progenitor cells from a subject, comprising implanting a Matrigel plug containing FGF-2 and heparin into mice that had undergone bone marrow transplants. The Matrigel plugs were injected subcutaneously near the abdominal midline, where it solidified to form a hydrogel. The implants were removed seven days after injection and were examined to show $CD34^+$ endothelial progenitor cells of donor origin had adhered to and incorporated in the implants.

Claims 1-7, 9-17, 21-24, 27-30, 39-40 and 42 lack an inventive step under PCT Article 33(3) as being obvious over Murayama et al (Exp Hematol, 2002) in view of Naughton et al (US 2003/0007654 A1), further in view of Nova et al (US Patent 6,340,588).

Murayama et al teach a method of isolating progenitor cells from a subject, comprising implanting a Matrigel plug containing FGF-2 and heparin into mice that had undergone bone marrow transplants. The Matrigel plugs were injected subcutaneously near the abdominal midline, where it solidified to form a hydrogel. The implants were removed seven days after injection and were examined to show $CD34^+$ endothelial cells of donor origin had adhered to and incorporated in the implants. Murayama et al does not teach including angiogenic/vasculogenic factor VEGF or a bone marrow recruiting factor.

Naughton et al teach a method for inducing vasculogenesis comprising implanting a 3-D stromal tissue implant that secretes a growth factor, thereby acting as a drug delivery device. The implant can comprise a mesh housing, a biodegradable polymer is contained within the housing. Angiogenic and/or vasculogenic growth factors can be contained within the biodegradable polymer. The angiogenic and/or vasculogenic growth factors can include VEGF, HGF, FGF, EGF, TGF, PDGF, and combinations thereof. The implant can be comprised in a vascular prosthesis in the vascular system in the heart, including the myocardium. It is intended for use in humans. Naughton et al does not teach including a bone marrow recruiting factor.

Nova et al teaches that VEGF, PDGF, and interleukins such as IL-8 and IL-1a (which applicant calls bone marrow recruiting factors) all promote vascularization when coated or otherwise included in an implantable device.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate progenitor cells, such as done by Murayama et al, substituting the Matrigel hydrogel with a 3-D stromal tissue implant device, such as taught by Naughton et al. One would have been motivated to use a more structured device such as that taught by Naughton et al in order to have more control over the placement of the implant, such as is required for use in humans. Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use angiogenesis and vasculogenesis growth factors such as VEGF, PDGF, HGF, FGF and bone marrow recruiting factors such as IL-8, IL-1a and other comparable factors as the growth factors comprised in the implant. One would have been motivated to use a combination of these angiogenesis/vasculogenesis

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

factors and bone marrow recruiting factors because they are taught to increase vasculogenesis around the implant.

Claims 1-43 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Claims 8, 18-20, 25-26, 31-38, 41 and 43 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of isolating recruiting progenitor cells to a bodily site in a subject, wherein the bodily site is removed from the vasculature, the implant comprises a drug delivery system housed in non-biodegradable mesh housing, wherein the implant comprises a polyanhydride polymer, or wherein the polymer is poly -L-lactide, PLGA, a poly (fumaric acid:sebacic acid) or polycaprolactone, wherein the bone marrow recruiting factor is GM-SCF, wherein the progenitor cells are further isolated and cultured and reintroduced into the subject, wherein the progenitor cells are $CD133^+$, or wherein the drug delivery system is prepared using phase inversion nanoencapsulation.